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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,057	07/06/2001	Fayad Z. Sheabar	4532660/29930	7817

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11/04/2003

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EXAMINER

PATTEN, PATRICIA A

ART UNIT

PAPER NUMBER

1654

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/900,057

Applicant(s)

SHEABAR ET AL.

Examiner

Patricia A Patten

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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SUPPLEMENTAL DETAILED ACTION

The finality of the Office Action dated 10/31/03 (Paper No. 7) is hereby removed in order to present the following rejection.

Claims 1-16 remain pending in the application and were examined on the merits.

Claim Objections

Claims 8 and 9 remain objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In the Instant case, claims 8 and 9 still recite inherent properties of the method without actually limiting claim 1.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention:

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Claims 1-16 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the Instant case, Applicant's have amended claim 1 to recite 'alcohol-free'.

It is pointed out that Applicants did not point out specifically in the Specification where this new limitation could be found. After a thorough review of the Specification, the Examiner cannot find support for the term 'alcohol-free'. Although the methods as disclosed in the Instant specification do not explicitly recite wherein alcohol is added to the extraction mixture, it cannot be clearly determined that Applicants had contemplated the breadth of the claimed invention, with the new limitation 'alcohol-free'. Therefore, it is deemed that the term 'alcohol-free' is New Matter, and Applicants are asked to remove this language from the claim in order to overcome this rejection.

Because claims 2-16 are either directly, or indirectly dependent upon claim 1, these claims contain all of the limitations of claim 1 and therefore also contain this New Matter and are henceforth rejected.

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All of Applicants' arguments pertain solely to the new limitation which recites 'alcohol-free'. These arguments are moot in light of the new rejections set forth *infra*.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5 and 7-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Borud (EP 0 487 480 A2).

Borud (EP 0487480 A2) disclosed a method for purification of a proteinase inhibitor which comprised separation of potato solids from the water-soluble liquid via high speed grating and sieving or centrifuging (col.3, lines 7-33). A summary of small - scale production of the proteinase inhibitors was discussed on col.5, lines 33-49: Hydrochloric acid (solvent) was added to the liquid potato extract to bring the pH to about 4.4 (col.5, lines 3-4 and lines 44-45). Proteins were coagulated by heating for 20 minutes at 65 °C (between about 60 and 90°C) followed by cooling to 20 C (col.5, lines 45-48).

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The coagulated (precipitated) proteins were removed via filtration (col.5, lines 48-49), and the remaining liquid (clarified extract solution) was concentrated via ultrafiltration with a DDS-FILTRATION equipment which employed a polysulfone membrane with an average pore size of 10 Å, MW cut off of about 10 kD (10 Å approximately equals 0.01 µm) (col.6, lines 25-29). The flux of the retentate was reported at 70 L permeate/m²/h (col.6, line 29) which approximately equals .11 L/ft²/min (1 m² = 10.76 ft²). Thus, it was clear from Borud that a membrane with a molecular weight cut-off with 10 kD (within the Instantly claimed range) would have allowed lower molecular weight molecules to traverse the membrane, while the protease inhibitors were forced back through into the retentate solution.

It is deemed that Borud heated the liquid fraction to a time sufficient to denature at least some of the other protein products without substantially denaturing the protease inhibitor because, as clearly indicated by Borud, "The process which is described here, aim[s] at extracting and concentrating the reasonably [heat-stable] inhibitors from the [potato-juice]" (col.4, lines 28-30). Here, Borud is referring to the 3 types of protease inhibitors as indicated at col.4, lines 22-27 which include chymotrypsin inhibitors, chymotrypsin and trypsin inhibitors and carboxypeptidase A and B inhibitors. Further, Borud states "After coagulation and removal of inactive proteins.." (col. 5, lines 53-54). Thus, it is clear that the goal of Borud was to heat the potato slurry (containing solids and liquids) to a temperature which would denature and precipitate unwanted proteins, but leave the proteins as described at col.4, lines 22-27. Here, Borud 'adjusted the

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temperature and time period of the heat treatment to selectively affect the purity and yield of the protease inhibitor' especially as evidenced by the statement "The heating to coagulation temperature is done continuously in a tube [heat exchanger] dimensioned for little overtemperatures on the heat-transporting surfaces to avoid local overheating which may destroy inhibitor proteins" (col.5, lines 10-13) and further gave a specific time range and temperature range in which to carry out the extraction as stated *supra*.

Absent any definition of the phrase 'about 30', it is deemed that 20 minutes is 'about 30 minutes'. Further, Borud clearly taught that the precipitate collected after coagulation (heating) was separated via decantercentrifuge (col.3, line 55-col.4 line 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borud as applied to claims 1, 4-5 and 7-12 above, and further in view of Pearce et al. (1983) or Bryant et al. (1976).

The teachings of Borud were discussed *supra*.

Borud did not teach wherein the protein slurry was heated to a temperature greater than about 75°C. Although Borud placed the protein slurry in a container which was heated to 80 °C; he stated that the proteins were only heated to about 70°C. As Borud explained, his intention was to isolate all of the proteases as displayed at col.4, lines 22-27 and therefore did not want to heat-denature any of these proteins.

Pearce et al. (1983) taught that carboxypeptidase inhibitors from potato tubers were heat stable to 80°C (p.223, col.2, 'Results and Discussion').

Bryant et al. (1976) taught that proteinase inhibitor II (trypsin/chymotrypsin inhibitor) from potatoes was heat stable at 80°C (p. 3419, col.2 'Isolation of Proteinase inhibitor II').

One of ordinary skill in the art would have been motivated to have heated the protein slurry to greater than about 75°C in order to have purified either carboxypeptidase inhibitor or proteinase inhibitor II. It was clear from Pearce et al. as well as Bryant et al. that both of these particular proteases were heat stable at 80°C and therefore, the ordinary artisan would have had a good expectation that heating to 80°C would have heat denatured many other proteins while saving these proteinase inhibitors.

Claims 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borud as applied to claims 1, 4-5 and 7-12 above, and further in view of Ryan et al. (WO 99/01474).

The teachings of Borud were discussed *supra*. Borud did not specifically teach wherein the protein was concentrated to 1/5 of the starting volume, wherein the clarified extract was added to ammonium bicarbonate prior to filtration, or wherein the filtration step further comprised washing with up to ten volumes of filtration buffer.

Ryan et al. (WO 99/01474) taught a method for isolating proteinase inhibitor II from potato tubers via extraction with a solvent (water/ethanol/.88% formic acid and 1.5 M NaCl), filtration via cheesecloth, heating the liquid portion to 70 °C, cooling, evaporation of ethanol, centrifugation and ultrafiltration via dialysis with 12-14 kD MW cutoff (p.9, Example 1 and claims 1-6). Ryan et al. taught that the precipitated proteins were advantageously dissolved in 0.1 M ammonium bicarbonate (p.8, lines 25-26). Ryan et al. mentioned that the addition of ammonium bicarbonate was 'suitable for solubilization and subsequent lyophilization - *a known method for stable storage of protease inhibitors*' (p.8, lines 25-27, emphasis added).

One of ordinary skill in the art would have been motivated to have concentrated the volume of the liquid protein slurry to 1/5 of the starting volume in order to de-salt the

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protein mixture in order to prepare the crude mixture for further purification such as column chromatography. The ordinary artisan would have recognized that the salt would need to be removed from solution in order to standardize the conductivity, thereby allowing the proteins to elute from the column based upon their respective ionic strengths.

One of ordinary skill in the art would have been motivated to wash the final protein product to remove any unwanted contaminants. Washing proteins with storage buffer was old and well known in the art of protein purification, as well as other forms of purification. The ordinary artisan would have had a reasonable expectation that washing the final protein precipitate would have 'cleaned-up' the protease, thereby creating a protease with greater activity as well as better stability upon storage.

One of ordinary skill in the art would have been motivated to add ammonium bicarbonate buffer prior to filtration in order to stabilize the protein thereby affecting a greater overall yield.

One of ordinary skill in the art would have been motivated to wash the final protein product to remove any unwanted contaminants. Washing proteins with storage buffer was old and well known in the art of protein purification, as well as other forms of purification. The ordinary artisan would have had a reasonable expectation that

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washing the final protein precipitate would have 'cleaned-up' the protease, thereby creating a protease with greater activity as well as better stability upon storage.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claims are allowed. Claims 2 and 3 are free of the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

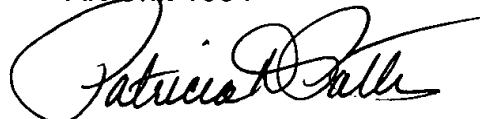
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A Patten whose telephone number is (703) 308-1189. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (703) 306-3220. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

10/28/03

Patricia A Patten
Examiner
Art Unit 1654

A handwritten signature in black ink, appearing to read 'Patricia A. Patten', written in a cursive style.

**PATRICIA PATTEN
PATENT EXAMINER**